

REVIEW ARTICLE

REVIEW ON: RECENT TREND ON TRANSDERMAL DRUG DELIVERY SYSTEM

*Shingade GM¹, Aamer Quazi¹, Sabale PM², Grampurohit ND², Gadhave MV², Jadhav SL², Gaikwad DD²¹K.T.Patil College of Pharmacy, Osmanabad, MH, INDIA -413501²Department of Pharmaceutics, Vishal Institute of Pharmaceutical Education & Research, Ale, Pune, MH, INDIA -412411*Corresponding Author's Email ID: pramodpharma21@gmail.com

Received 03 Dec 2011; Revised 05 Jan 2012; Accepted 10 Jan 2012, Available online 20 Jan 2012

ABSTRACT

Today about 74% of drugs are taken orally and are found not to be as effective as desired. To improve such characters transdermal drug delivery system was emerged. Drug delivery through the skin to achieve a systemic effect of a drug is commonly known as transdermal drug delivery and differs from traditional topical drug delivery. Transdermal drug delivery systems (TDDS) are dosage forms involves drug transport to viable epidermal and or dermal tissues of the skin for local therapeutic effect while a very major fraction of drug is transported into the systemic blood circulation. The adhesive of the transdermal drug delivery system is critical to the safety, efficacy and quality of the product. Topical administration of therapeutic agents offers many advantages over conventional oral and invasive methods of drug delivery. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug.

Keywords: TDDS, Topical drug delivery, Systemic blood circulation.

INTRODUCTION

Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively¹. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. The first Transdermal system, Transderm-SCOP was approved by FDA in 1979 for the prevention of nausea and vomiting associated with ravel, particularly by sea. The evidence of percutaneous drug absorption may be found through measurable blood levels of the drug, detectable excretion of the drug and its metabolites in the urine and through the clinical response of the patient to the administered drug therapy.² The common ingredients which are used for the preparation of TDDS are as follows.³

- Drug: Drug is in direct contact with release liner.Ex: Nicotine, Methotrexate and Estrogen.

- Liners: Protects the patch during storage. Ex: polyester film.
- Adhesive: Serves to adhere the patch to the skin for systemic delivery of drug.
Ex: Acrylates, Polyisobutylene, Silicones.
- Permeation enhancers: Controls the Release of the drug. Ex: Terpenes, Terpenoids, Pyrrolidones.Solvents like alcohol, Ethanol, Methanol.Surfactants like Sodium Lauryl sulfate, Pluronic F127, Pluronic F68.
- Backing layer: Protect patch from outer environment. Ex: Cellulose derivatives, poly vinyl alcohol, Polypropylene Silicon rubber.

Advantages of Transdermal Drug Delivery System (TDDS)

The advantages of transdermal delivery over other delivery systems are as follows:

1. Avoidance of first pass metabolism of drugs.
2. Reduced plasma concentration levels of drugs, with decreased side effects.
3. Reduction of fluctuations in plasma levels of drugs, Utilization of drug candidates with short half-life and low therapeutic index.
4. Easy elimination of drug delivery in case of toxicity.
5. Reduction of dosing frequency an enhancement of patient compliance.
6. Transdermal medications deliver a steady infusion of a drug over and extended period of time. Adverse effects

or therapeutic failure frequently associated with intermittent dosing can also be avoided.

7. Transdermal delivery can increase the therapeutic value of many drugs via avoiding specific problems associated with the drug. E.g. GI irritation, lower absorption, decomposition due to 'hepatic first pass' effect.
8. Due to above advantage, it is possible that an equivalent therapeutic effect can be elicited via transdermal drug input with a lower daily dose of the drug than is necessary, if e.g. the drug is given orally.
9. The simplified medication regimen leads to improved patient compliance and reduced inter and intra-patient variability.

Limitation of TDDS

The drug must have some desirable physicochemical properties for penetration through stratum corneum and if the drug dosage required for therapeutic value is more than 10 mg/day, the transdermal delivery will be very difficult if not impossible. Skin irritation or contact dermatitis due to the drug, excipients and enhancers of the drug used to increase percutaneous absorption is another limitation. Clinical need is another area that has to be examined carefully before a

decision is made to develop a transdermal product. The barrier function of the skin changes from one site to another on the same person, from person to person and with age.

Limitations for a drug substance to be incorporated into a transdermal delivery system are: -

- Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- Drugs that are highly melting can be given by this route due to their low solubility both in water and fat.³
- Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy.

The major considerations for enhancing transdermal delivery are physical enhancers (ultrasound, iontophoresis, electroporation, magnetophoresis, microneedle), vesicles, particulate systems (liposome, niosome, transfersome, microemulsion, solid lipid nanoparticle) and chemical enhancers (sulphoxides, azones, glycols, alkanols, terpenes etc.).⁴

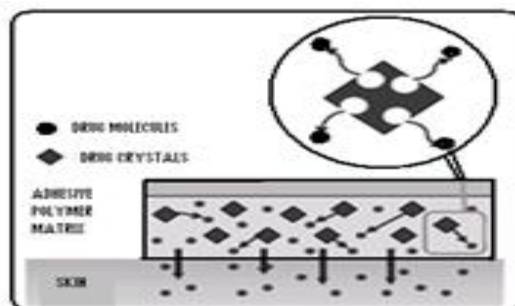


Figure 1: Crystal reservoir technology has resulted in smaller patches with a more controlled and sustained drug release

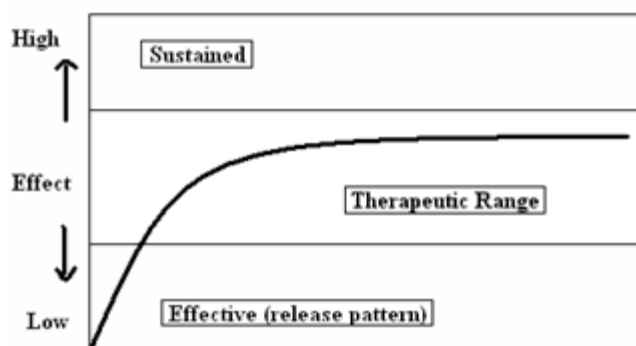


Figure 2: Sustained release is facilitated through the consistent rejuvenation of drug molecules at the surface of skin

Along with A number of drugs may be administered by transdermal route. Transdermal drug absorption markedly alters drug kinetics and depends on a several parameters including the following-

- Medicament application site
- Thickness and integrity of the stratum cornea epidermidis.
- Size of the molecule that is to be administered.

- Permeability of the membrane for the transdermal drug delivery.
- Hydration state of skin.
- pH of the drug.
- Drug metabolism by skin flora.
- Lipid solubility.
- Drug depot in skin.

- Blood flow alteration in the skin by additives and body temperature

The toxic effect of the drug and problem in limiting drug uptake are major considerable potential for transdermal delivery systems, especially in children because skin thickness and blood flow in the skin usually vary with age. The increased blood supply in the skin along with thinner skin has significant effects on the pharmacokinetics of transdermal delivery for children. In some situations this may be an advantageous, while in others systemic toxicity may occur. This was observed after using scopolamine patches that are used to prevent motion sickness, a eutectic mixture of local anesthetics (EMLA) cream used to minimize the pain, corticosteroid cream applied for its local effect on skin maladies. Episodes of systemic toxic effects, including some fatalities in children have been documented with each of these, often secondary to accidental absorption through mucous membranes⁵.

Limitations for a drug substance to be incorporated into a transdermal delivery system are: -

- Heavy drugs molecules (>500 Da) usually difficult to penetrate the stratum cornea.
- Drugs with very low or high partition coefficient fail to reach blood circulation.
- Drugs that are highly melting can be given by this route due to their low solubility both in water and fat¹.

Many approaches have been attempted to deliver medicament across skin barrier and enhance the efficacy. The major considerations for enhancing transdermal delivery are physical enhancers (ultrasound, iontophoresis, electroporation, magnetophoresis, microneedle), vesicles, particulate systems (liposome, niosome, transfersome, microemulsion, solid lipid nanoparticle) and chemical enhancers (sulphoxides, azones, glycols, alkanols, terpenes etc.).⁶

1. Tdds Classification Based On Their Technical Sophistication

- a) Rate pre-programmed drug delivery system
- b) Activation modulated drug delivery system
- c) Feedback regulated drug delivery system
- d) Carrier based drug delivery system

A) Rate Pre Programmed Drug Delivery System

It involves the system design that delivers medicaments by controlling molecular diffusion of drug molecules across the skin barrier within or surrounding the delivery system.

1. Polymer membrane permeation controlled drug delivery system-

It involves the system in which the drug is enclosed within a drug reservoir. This is covered by the semi permeable membrane of polymer that regulates the release and having a specific permeability. There are some potential development with process of membrane permeation are as microporous membrane permeation controlled gastrointestinal delivery

device, gastric fluid resistance intestinal targeted controlled release gastrointestinal device and gel diffusion controlled drug delivery system.⁷

2. Polymer matrix diffusion controlled drug delivery system-

It is developed by dispersing drug particles in carrier matrix (in a homogenous manner) that is rate controlling i.e. NitroDur. It is designed for application onto intact skin for 24 hrs that provide consistence transdermal infusion of nitroglycerine.⁸

3. Microreservoir partitioned controlled drug delivery system-

It involves dispersion of micro particles of suspension of drug (aqueous in nature) in a polymer using high energy dispersion. e.g. Syncromate implant. Engineered to deliver subdermal administration of norgestomet.⁸

B) Activation Modulated Drug Delivery System

This type of delivery system can be achieved by-

1-Physical means

- Osmotic pressure activated drug delivery system.
- Hydrodynamic pressure controlled drug delivery system.
- Vapour pressure activated drug delivery system.
- Mechanically activated drug delivery system.
- Magnetically activated drug delivery system.
- Electrically activated drug delivery system.
- Ultrasound activated drug delivery system.
- Hydration activated drug delivery system.

2-Chemical means

- pH activated drug delivery system
- Ion activated drug delivery system
- Hydrolysis activated drug delivery system

3-Biochemical means

- Enzymes activated drug delivery system

C) Feedback Regulated Drug Delivery System

The release of the drug molecules from the transdermal system is facilitated by a agent that triggers the release of drug, such as biochemicals in the body and also regulated by its concentration through some feedback mechanism.

- Bio-erosion regulated drug delivery system.
- Bio-responsive drug delivery system.
- Self regulated drug delivery system.⁹

D) Carrier Based Drug Delivery System

Colloidal particulates carrier system:

This involves vesicular system like hydrogels, liposomes, niosomes, nanocapsules, nanoparticles, polymeric complexes, microspheres, nanoerythrocytes, transferosomes, dendrimers, aquasomes, etc.

RECENT TECHNIQUES FOR ENHANCING TDDS

A) STRUCTURE-BASED ENHANCEMENT TECHNIQUES:

1. Transdermal Patches

A transdermal patch or skin adhesive patch is that device which is loaded with drug candidate and usually applied on the skin to transport a specific dose of medication across the skin and into the blood circulation.¹⁰

The adhesive serves two functions: It is glue in nature that keeps the patch adhered to the skin, and it acts as the suspension that holds the drug. The problems associated with this is the concentration of the drug within the adhesive directly affects the "stickiness" of the adhesive so if the large quantities of drug is to be administered, either the size of the patch have to be increased or the patch needs to be reapplied

again and again. Several pharmaceuticals usually combined with substances, like alcohol, within the patch to improve their penetration via skin in order to improve absorption.¹¹

Components of Transdermal Patch:-

Liner - Protects the patch during storage. The liner should be removed before its use.

Drug- Drug solution is in direct contact with release liner.

Adhesive- It serves to adhere the components of the patch together along with adhering the patch to the skin. E.g.- Acrylic, polyisobutylene (PIB), and silicone are the adhesives have many pharmaceutical applications. For applications in which the adhesive, the drug, and perhaps enhancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).

Membrane- It controls the release of the drug from the reservoir and multi-layer patches.

Backing- The film protects the patch from the outer environment¹²⁻¹³.

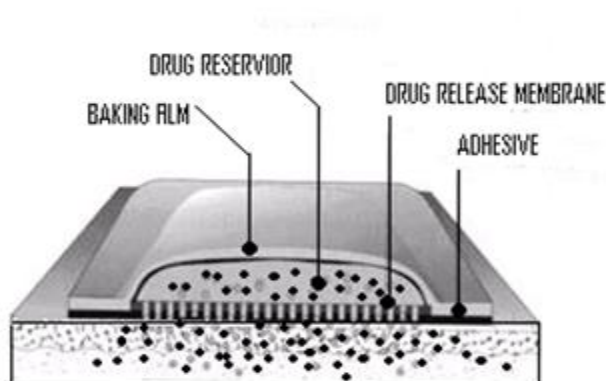


Figure 3: Different parts of Transdermal Patch

Requirements for pressure-sensitive adhesives (PSAs)

Several classes of PSAs are used for skin contact application include acrylics, polyisobutylene and silicone polymers.¹⁶ The functional properties of PSAs such as tackiness, adhesive property, release force, and cohesive strength as well as adhesive formulations having attributes such as enhanced drug flux and skin friendliness. A PSA must be able to performance effectively under a wide range of temperatures, humidity levels, and application frequency (from 24 hrs for some products to one week for others). The effects of mechanical stresses (e.g., stretching) as well as skin irritation and sensitization also must be considered.²¹ The human studies of various commercially available transdermals are examined and reported to assess the relative performance capabilities of each type of transdermal design.²⁴ Monolithic TTS was fabricated in PSAs- (a)

terpolymer (PSA1) of 2-ethylhexyl acrylate, methyl methacrylate, and acrylic acid, (b) copolymer (PSA2) of 2-ethylhexyl acrylate, methyl methacrylate, acrylic acid, and vinyl acetate, and (c) Eudragit E100 pressure sensitive adhesive (PSA3). The transport of nicorandil via skin can be achieved by the skin permeation enhancer i.e. *N*-methyl-2-pyrrolidone (NMP) was investigated at different concentrations (5%) in PSAs¹⁷

2. Microfabricated Microneedles

These are the devices which are having the features of both the hypodermic needle and transdermal patch that can deliver the drug that transports the drug effectively across the membrane. The systems consists of a drug reservoir and a some projections (microneedles) extending from the reservoir, these helps in penetrating the stratum cornea and epidermis to deliver the drug.

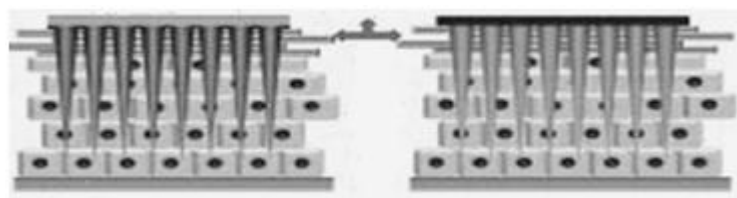


Figure 4: Delivery site for microneedle technology. (a) Hollow microneedles with applied formulation; (b) Solid microneedles. Microneedles are tiny and very sleek devices that are manufactured by the silicon etching technology and micro-mechanical system manufacturing (MEMS) technique, which do not penetrate deep enough into the skin to reach up to the nerve endings and thus there is no pain sensation during the microneedles insertion into the skin. There are number of delivery approaches that have been employed to use the microneedles for TDDS. These includes-

Poke with patch approach- Involves piercing into the skin followed by application of the drug patch at the site of treatment.

Coat and poke approach- Needles coated with the drug are inserted into the skin and release of medicament is then occurs by dissolution.

Biodegradable microneedles- Involves encapsulation of the drug within the biodegradable, polymeric microneedles, which is then inserted into the skin.

Hollow microneedles- Involves injecting the drug through the needle with a hollow bore.³⁰

3. Macroflux

These are devices having an area of around 8cm² as well as 300 micro projections per cm² with the length of individual micro projection less than 200 μ m. Three types of Macroflux have been designed. They include, Dry-Coated Macroflux system-this is used for short period delivery that consists microprojection array coated with medicament that adhered to a elastic polymer adhesive backing.

4. Metered-Dose Transdermal Spray (MdtS)

It is a liquid preparation in the form of solution that are used topically which is made up of a vehicle that is volatile come non volatile in nature, which consists the completely dissolved medicament in solution. The use of MDTs reaches the sustained level and better permeation of the drug via skin. The MDTs has the following potential advantages:

- It improves delivery potential without skin irritation due to its non-occlusive nature.
- Increased acceptability.
- Dose flexibility
- Simple manufacture¹.

B) ELECTRICALLY-BASED ENHANCEMENT TECHNIQUES:

1. Iontophoresis

It involves passing of current (few milliamperes) to skin limited to a certain area using the electrode remains in contact with the formulation which is to be administered. Pilocarpine delivery can be taken as example to induce sweat in the diagnosis of cystic fibrosis and Iontophoretic delivery

of lidocaine is considered to be a nice approach for rapid onset of anesthesia.^{18, 19}

2. Ultrasound

In this technique, there is a mixing of drug substance with a coupling agent (usually with gel, cream or ointment) that causes ultrasonic energy transfer from the system to the skin. This involves rupturing the lipids present in stratum cornea, which allows the medicament to permeate via biological barrier.

3. Photomechanical Waves

Photomechanical waves significantly led to the stratum cornea highly permeable to drug substance through a possible permeabilisation mechanism due to development of transient channels.

4. Electroporation

In this method, short and high-voltage electrical pulses are applied to the skin thus the diffusion of drug is improved with the increasing permeability. The electrical pulses are considered to form small pores in the stratum cornea, through which transportation of drug occurs. For the safe and painless administration, the electrical pulses introduced by closely spaced electrodes to reserved the electric field within the stratum cornea.^{18, 20, 21, 22}

5. Electro-Osmosis

To the porous membrane which is having some charge, a voltage difference is applied to it, thus a bulk fluid or volume flow takes place with no concentration gradients. This process is known as electro-osmosis.

C). VELOCITY BASED ENHANCEMENT TECHNIQUES:

1. Needle-Free Injections

- Intraject
- Implaject
- Jet Syringe
- Iject
- Mini-ject

2. Powderject Device

The solid drug particles are propelled across the skin with the aid of high-speed gas flow. This consists of a gas canister that allows helium gas at high pressure to enter a chamber at

the end of which drug cassette containing powdered drug between two polycarbonate membranes. After release, the instantaneous rupture of both membranes usually seen that results in the gas to expand quickly which forms a strong motion like a wave that travels down the nozzle. This takes place at the speed of 600-900 m/s.

D) OTHER ENHANCEMENT TECHNIQUES:

1. Transfersomes-

This device penetrates the skin barrier along the skin moisture gradient. Transfersome carriers can create a drug depot in the systemic circulation that is having a high concentration of drug. Transfersomes contain a component that destabilizes the lipid bilayers and thus leading to the deformable vesicles.

2. Medicated Tattoos-

Med-Tats is a modification of temporary tattoo which contains an active drug substance for transdermal delivery. This technique is useful in the administration of drug in those children who are not able to take traditional dosage forms.

3. Skin Abrasion-

This involves direct removal or disruption of the upper layers of the skin to provide better permeation of topically applied drug substance. In general, one approach is adopted to create micro channels in the skin by eroding the impermeable outer layers with sharp microscopic metal granules is generally known as Microdissection.

4. Controlled Heat Aided Drug Delivery (CHADD) System-

It facilitates the transfer of drug substance to the blood circulation by applying heat to the skin that increases the temperature and ultimately led to increase in microcirculation and permeability in blood vessel. CHADD system consists of small unit that is used for heating purpose, placed on top of a conventional patch device. An oxidation reaction occurs within the unit which tends to form heat of limited intensity and duration.

5. Laser Radiation-

This involves the exposure of the skin to the laser beam that results in the ablation of the stratum corneum without damaging the epidermis which remains in contact with it. Removal of the stratum corneum by this technique is considered to improve the delivery of lipophilic and hydrophilic drugs.

6. Magnetophoresis-

The effect of magnetic field on diffusion flux of drug substance was found to enhance with increasing applied strength.¹

TYPES OF TRANSDERMAL PATCHES: ⁴⁻⁸

a) Single layer drug in adhesive:

In this type the adhesive layer contains the drug. The adhesive layer not only serves to adhere the various layers together and also responsible for the releasing the drug to the

skin. The adhesive layer is surrounded by a temporary liner and a backing.

b) Multi-layer drug in adhesive:

This type is also similar to the single layer but it contains an immediate drug release layer and other layer will be a controlled release along with the adhesive layer. The adhesive layer is responsible for the releasing of the drug. This patch also has a temporary liner-layer and a permanent backing.

c) Vapour patch:

In this type of patch the role of adhesive layer not only serves to adhere various layers together but also serves as release vapour. The vapour patches are new to the market, commonly used for releasing of essential oils in decongestion. Various other types of vapor patches are also available in the market which are used to improve the quality of sleep and reduces the cigarette smoking conditions.

d) Reservoir system:

In this system the drug reservoir is embedded between an impervious backing layer and a rate controlling membrane. The drug releases only through the rate controlling membrane, which can be micro porous or non porous. In the drug reservoir compartment, the drug can be in the form of a solution, suspension, gel or dispersed in a solid polymer matrix. Hypoallergenic adhesive polymer can be applied as outer surface polymeric membrane which is compatible with drug.

e) Matrix system:

i. Drug-in-adhesive system:

In this type the drug reservoir is formed by dispersing the drug in an adhesive polymer and then spreading the medicated adhesive polymer by solvent casting or melting (in the case of hot-melt adhesives) on an impervious backing layer. On top of the reservoir, unmediated adhesive polymer layers are applied for protection purpose.

ii. Matrix-dispersion system:

In this type the drug is dispersed homogeneously in a hydrophilic or lipophilic polymer matrix. This drug containing polymer disk is fixed on to an occlusive base plate in a compartment fabricated from a drug impermeable backing layer. Instead of applying the adhesive on the face of the drug reservoir, it is spread along with the circumference to form a strip of adhesive rim.

f) Microreservoir system:

In this type the drug delivery system is a combination of reservoir and matrix-dispersion system. The drug reservoir is formed by first suspending the drug in an aqueous solution of water soluble polymer and then dispersing the solution homogeneously in a lipophilic polymer to form thousands of unreachably, microscopic spheres of drug reservoirs. This thermodynamically unstable dispersion is stabilized quickly by immediately cross-linking the polymer in situ by using cross linking agents.

VARIOUS METHODS FOR PREPARATION TDDS:**a. Asymmetric TPX membrane method:**²³

A prototype patch can be fabricated for this a heat sealable polyester film (type 1009, 3m) with a concave of 1cm diameter will be used as the backing membrane. Drug sample is dispensed into the concave membrane, covered by a TPX {poly(4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive.

b. Circular teflon mould method:²⁴

Solutions containing polymers in various ratios are used in an organic solvent. Calculated amount of drug is dissolved in half the quantity of same organic solvent. Enhancers in different concentrations are dissolved in the other half of the organic solvent and then added. Di-N-butylphthalate is added as a plasticizer into drug polymer solution. The total contents are to be stirred for 12 hrs and then poured into a circular teflon mould. The moulds are to be placed on a leveled surface and covered with inverted funnel to control solvent vaporization in a laminar flow hood model with an air speed of 0.5 m/s. The solvent is allowed to evaporate for 24 hrs. The dried films are to be stored for another 24 hrs at $25 \pm 0.5^\circ\text{C}$ in a desiccators containing silica gel before evaluation to eliminate aging effects. The type films are to be evaluated within one week of their preparation.

c. Mercury substrate method:²⁵

In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10-15 minutes to produce a homogenous dispersion and poured in to a leveled mercury surface, covered with inverted funnel to control solvent evaporation.

d. By using IPM membranes" method:²⁶

In this method drug is dispersed in a mixture of water and propylene glycol containing carbomer 940 polymer and stirred for 12 hrs in magnetic stirrer. The dispersion is to be neutralized and made viscous by the addition of triethanolamine. Buffer pH 7.4 can be used in order to obtain solution gel, if the drug solubility in aqueous solution is very poor. The formed gel will be incorporated in the IPM membrane.

e. By using EVAC membranes" method:²⁷

In order to prepare the target transdermal therapeutic system, 1% carbopol reservoir gel, polyethylene (PE), ethylene vinyl acetate copolymer (EVAC) membranes can be used as rate control membranes. If the drug is not soluble in water, propylene glycol is used for the preparation of gel. Drug is dissolved in propylene glycol; carbopol resin will be added to the above solution and neutralized by using 5% w/w sodium hydroxide solution. The drug (in gel form) is placed on a sheet of backing layer covering the specified area. A rate controlling membrane will be placed over the gel and the edges will be sealed by heat to obtain a leak proof device.

f. Aluminium backed adhesive film method:²⁸

Transdermal drug delivery system may produce unstable matrices if the loading dose is greater than 10 mg. Aluminium

backed adhesive film method is a suitable one. For preparation of same, chloroform is choice of solvent, because most of the drugs as well as adhesive are soluble in chloroform. The drug is dissolved in chloroform and adhesive material will be added to the drug solution and dissolved. A custom made aluminium former is lined with aluminium foil and the ends blanked off with tightly fitting cork blocks.

g. Preparation of TDDS by using Proliposomes:^{29,30}

The proliposomes are prepared by carrier method using film deposition technique. From the earlier reference drug and lecithin in the ratio of 0.1:2.0 can be used as an optimized one. The proliposomes are prepared by taking 5mg of mannitol powder in a 100 ml round bottom flask which is kept at $60-70^\circ\text{C}$ temperature and the flask is rotated at 80-90 rpm and dried the mannitol at vacuum for 30 minutes. After drying, the temperature of the water bath is adjusted to $20-30^\circ\text{C}$. Drug and lecithin are dissolved in a suitable organic solvent mixture, a 0.5ml aliquot of the organic solution is introduced into the round bottomed flask at 37°C , after complete drying second aliquots (0.5ml) of the solution is to be added. After the last loading, the flask containing proliposomes are connected in a lyophilizer and subsequently drug loaded mannitol powders proliposomes) are placed in a desiccator over night and then sieved through 100 mesh. The collected powder is transferred into a glass bottle and stored at the freeze temperature until characterization.

h. By using free film method:³¹

Free film of cellulose acetate is prepared by casting on mercury surface. A polymer solution 2% w/w is to be prepared by using chloroform. Plasticizers are to be incorporated at a concentration of 40% w/w of polymer weight. Five ml of polymer solution was poured in a glass ring which is placed over the mercury surface in a glass petri dish. The rate of evaporation of the solvent is controlled by placing an inverted funnel over the Petri dish. The film formation is noted by observing the mercury surface after complete evaporation of the solvent. The dry film will be separated out and stored between the sheets of wax paper in a desiccator until use. Free films of different thickness can be prepared by changing the volume of the polymer solution.

EVALUATION PARAMETERS:**1. Interaction studies:**^{31,32}

Excipients are integral components of almost all pharmaceutical dosage forms. The stability of a formulation amongst other factors depends on the compatibility of the drug with the excipients. The drug and the excipients must be compatible with one another to produce a product that is stable, thus it is mandatory to detect any possible physical or chemical interaction as it can affect the bioavailability and stability of the drug. If the excipients are new and have not been used in formulations containing the active substance, the compatibility studies play an important role in formulation development. Interaction studies are commonly carried out in Thermal analysis, FT-IR, UV and chromatographic techniques by comparing their

physicochemical characters such as assay, melting endotherms, characteristic wave numbers, absorption maxima etc.,

2. Thickness of the patch:³³

The thickness of the drug loaded patch is measured in different points by using a digital micrometer and determines the average thickness and standard deviation for the same to ensure the thickness of the prepared patch.

3. Weight uniformity:³³

The prepared patches are to be dried at 60°C for 4hrs before testing. A specified area of patch is to be cut in different parts of the patch and weigh in digital balance. The average weight and standard deviation values are to be calculated from the individual weights.

4. Folding endurance:³³

A strip of specific area is to be cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the value of the folding endurance.

5. Percentage Moisture content:³³

The prepared films are to be weighed individually and to be kept in a desiccator containing fused calcium chloride at room temperature for 24 hrs. After 24 hrs the films are to be reweighed and determine the percentage moisture content from the below mentioned formula. Percentage moisture content = $\frac{\text{Initial weight} - \text{Final weight}}{\text{Final weight}} \times 100$.

6. Percentage Moisture uptake:³³

The weighed films are to be kept in a desiccator at room temperature for 24 hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24 hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula. Percentage moisture uptake = $\frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$.

7. Water vapour permeability (WVP) evaluation:³²

Water vapour permeability can be determined with foam dressing method the air forced oven is replaced by a natural air circulation oven. The WVP can be determined by the following formula $WVP = \frac{W}{A}$ Where, WVP is expressed in gm/m² per 24hrs, W is the amount of vapour permeated through the patch expressed in gm/24hrs and A is the surface area of the exposure samples expressed in m².

8. Drug content:³²

A specified area of patch is to be dissolved in a suitable solvent in specific volume. Then the solution is to be filtered through a filter medium and analyse the drug content with the suitable method (UV or HPLC technique). Each value represents average of three different samples.

9. Uniformity of dosage unit test:³³

An accurately weighed portion of the patch is to be cut into small pieces and transferred to a specific volume volumetric flask, dissolved in a suitable solvent and sonicate for

complete extraction of drug from the patch and made up to the mark with same. The resulting solution was allowed to settle for about an hour, and the supernatant was suitably diluted to give the desired concentration with suitable solvent. The solution was filtered using 0.2 µm membrane filter and analysed by suitable analytical technique (UV or HPLC) and the drug content per piece will be calculated.

10. Polariscopes examination:³³

This test is to be performed to examine the drug crystals from patch by polariscopes. A specific surface area of the piece is to be kept on the object slide and observe for the drugs crystals to distinguish whether the drug is present as crystalline form or amorphous form in the patch.

11. Shear Adhesion test:³³

This test is to be performed for the measurement of the cohesive strength of an adhesive polymer. It can be influenced by the molecular weight, the degree of crosslinking and the composition of polymer, type and the amount of tackifier added. An adhesive coated tape is applied onto a stainless steel plate; a specified weight is hung from the tape, to affect it pulling in a direction parallel to the plate. Shear adhesion strength is determined by measuring the time it takes to pull the tape off the plate. The longer the time take for removal, greater is the shear strength.

12. Peel Adhesion test:³³

In this test, the force required to remove an adhesive coating from a test substrate is referred to as peel adhesion. Molecular weight of adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and then tape is pulled from the substrate at a 180° angle, and the force required for tape removed is measured. Peel adhesion is the force required to remove an adhesive coating from a test substrate. Adhesive should provide adequate contact of the device with the skin and should not damage the skin on removal. Peel adhesion properties are affected by the molecular wt of the adhesive polymer, the type and amount of additives, and polymer composition. It is tested by measuring the force required to pull a single coated tape, applied to a substrate, at a 180° angle. No residue on the substrate indicates 'adhesive failure' which is desirable for transdermal devices. Remnants on the substrate indicate 'cohesive failure' signifying a deficit of cohesive strength in the coating.

13. Thumb tack test:

It is a qualitative test applied for tack property determination of adhesive. The thumb is simply pressed on the adhesive and the relative tack property is detected.

14. Flatness test:³⁴

Three longitudinal strips are to be cut from each film at different portions like one from the center, other one from the left side, and another one from the right side. The length of each strip was measured and the variation in length because of non-uniformity in flatness was measured by determining

percent constriction, with 0% constriction equivalent to 100% flatness.

15. Percentage Elongation break test:³⁵

The percentage elongation break is to be determined by noting the length just before the break point, the percentage elongation can be determined from the below mentioned formula. $\text{Elongation percentage} = \frac{L_1 - L_2}{L_2} \times 100$. Where, L_1 is the final length of each strip and L_2 is the initial length of each strip.

16. Rolling ball tack test:³⁶

This test measures the softness of a polymer that relates to tack. In this test, stainless steel ball of 7/16 inches in diameter is released on an inclined track so that it rolls down and comes into contact with horizontal, upward facing adhesive. The distance the ball travels along the adhesive provides the measurement of tack, which is expressed in inch.

17. Quick Stick (peel-tack) test:³⁶

In this test, the tape is pulled away from the substrate at 90°C at a speed of 12 inches/min. The peel force required to break the bond between adhesive and substrate is measured and recorded as tack value, which is expressed in ounces or grams per inch width.

18. Probe Tack test:³⁶

In this test, the tip of a clean probe with a defined surface roughness is brought into contact with adhesive, and when a bond is formed between probe and adhesive. The subsequent removal of the probe mechanically breaks it. The force required to pull the probe away from the adhesive at fixed rate is recorded as tack and it is expressed in grams.

19. In vitro drug release studies:³⁷

The paddle over disc method (USP apparatus V) can be employed for assessment of the release of the drug from the prepared patches. Dry films of known thickness is to be cut into definite shape, weighed, and fixed over a glass plate with an adhesive. The glass plate was then placed in a 500-mL of the dissolution medium or phosphate buffer (pH 7.4), and the apparatus was equilibrated to $32 \pm 0.5^\circ\text{C}$. The paddle was then set at a distance of 2.5 cm from the glass plate and operated at a speed of 50 rpm. Samples (5- mL aliquots) can be withdrawn at appropriate time intervals up to 24 h and analyzed by UV spectrophotometer or HPLC. The experiment is to be performed in triplicate and the mean value can be calculated.

20. In vitro skin permeation studies:³⁷

An in vitro permeation study can be carried out by using diffusion cell. Full thickness abdominal skin of male Wistar rats of weighing 200 to 250g. Hair from the abdominal

region is to be removed carefully by using a electric clipper; the dermal side of the skin was thoroughly cleaned with distilled water to remove any adhering tissues or blood vessels, equilibrated for an hour in dissolution medium or phosphate buffer pH 7.4 before starting the experiment and was placed on a magnetic stirrer with a small magnetic needle for uniform distribution of the diffusant. The temperature of the cell was maintained at $32 \pm 0.5^\circ\text{C}$ using a thermostatically controlled heater. The isolated rat skin piece is to be mounted between the compartments of the diffusion cell, with the epidermis facing upward into the donor compartment. Sample volume of definite volume is to be removed from the receptor compartment at regular intervals, and an equal volume of fresh medium is to be replaced. Samples are to be filtered through filtering medium and can be analyzed spectrophotometrically or HPLC. Flux can be determined directly as the slope of the curve between the steady-state values of the amount of drug permeated (mg cm^{-2}) vs. time in hours and permeability coefficients were deduced by dividing the flux by the initial drug load (mg cm^{-2}).

21. Skin Irritation study:³³

Skin irritation and sensitization testing can be performed on healthy rabbits (average weight 1.2 to 1.5 kg). The dorsal surface (50 cm^2) of the rabbit is to be cleaned and remove the hair from the clean dorsal surface by shaving and clean the surface by using rectified spirit and the representative formulations can be applied over the skin. The patch is to be removed after 24 hr and the skin is to be observed and classified into 5 grades on the basis of the severity of skin injury.

22. Stability studies:³⁷

Stability studies are to be conducted according to the ICH guidelines by storing the TDDS samples at $40 \pm 0.5^\circ\text{C}$ and $75 \pm 5\%$ RH for 6 months. The samples were withdrawn at 0, 30, 60, 90 and 180 days and analyze suitably for the drug content.

CONCLUSION

This article provides an valuable information regarding the transdermal drug delivery systems and its evaluation process. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs. To optimize this drug delivery system, greater understanding of the different mechanisms of biological interactions, and polymer are required. TDDS a realistic practical application as the next generation of drug delivery system

1. Loyd V. Allen Jr, Nicholas G. Popovich, Howard C. Ansel. Pharmaceutical dosage forms and drug delivery systems, 8th Edition., Wolter Kluwer Publishers, New Delhi, 2005 pp. 298-299.
2. Kumar P, Sankar C, Mishra B. Delivery of macromolecules through skin. The Indian Pharmacist 2004;5(3): 7-17.
3. Kumar R, Philip A. Modified Transdermal Technologies: Breaking the Barriers of Drug Permeation via the Skin. Trop J Pharm Res. 2007, 6(1):633-644.
4. Rizwan M, Aqil M, Talegoankar S, Azeem A, Sultana Y, Ali A. Enhanced transdermal drug delivery techniques: an extensive review on patents. Recent Pat Drug Deliv&formul. 2009, 3(2):105-24.
5. Cheston M. Berlin. Clinical report- Alternative Routes of Drug Administration- Advantages & Disadvantages (subject review). Pediatrics 1997.
6. Rizwan M, Aqil M, Talegoankar S, Azeem A, Sultana Y, Ali A. Enhanced transdermal drug delivery techniques: an extensive review on patents. Recent Pat Drug Deliv&formul. 2009, 3(2):105-24.
7. Weiner E, Victor A, Johansson ED. Plasma levels of d-Norgestrel after oral administration. Contraception 1976, 14: 563-570.
8. Keith AD, Polymer matrix consideration for Transdermal Devices. Drug DevInd Pharm. 1983, 9: 605-625.
9. Karim A. Transdermal absorption: a unique opportunity for constant delivery of nitroglycerin. Drug DevInd Pharm. 1983, 9: 671.
10. Helier J, Trescony PV. Controlled drug release by polymer dissolution II, Enzyme mediated delivery device. J. Pharm. Sci. 1979, 68: 919.
11. <http://www.pharmainfo.net/reviews/transdermal-drug-delivery-technology-revisited-recent-advances>
12. <http://www.pharmainfo.net/jasmine-jose/transdermal-patches-innovative-technology>
13. Hopp SM. Developing Custom Adhesive Systems for Transdermal Drug Delivery Products. Pharmaceutical Technology 2002, 30-36.
14. <http://ezinearticles.com/?Transdermal-Drug-Delivery,-Transdermal-Patches&id=155961>
15. Hopp SM. Developing Custom Adhesive Systems for Transdermal Drug Delivery Products. Pharmaceutical Technology 2002, 30-36
16. Grossberg GT, Sadowsky C, Olin JT. Rivastigmine Transdermal System for the Treatment of Mild to Moderate Alzheimer's Disease. Int J ClinPract. 2010, 64(5): 651-660.
17. Venkatraman S, Gale R. Skin adhesives and skin adhesion. 1. Transdermal drug delivery systems. Biomaterials 1998, 19(13): 1119-36
18. Tiple ND & Vavia RP. Formulation Optimization and Stability Study of Transdermal Therapeutic System of Nicorandil. Informa Healthcare 2002, 7(3):325-332.
19. Calhoun A Darlene et al. Recent Advances in Neonatal Pharmacotherapy: Transdermal Therapy in Neonates. Ann. Pharmacother. 2006, 40 (4): 710-719.
20. <http://www.theiaforum.org/april2004.htm>
21. Sugar IP, Neumann E. Stochastic model for electric field-induced membrane pores. Electroporation. Biophys. Chem. 1984, 19(3): 211. 25.
22. http://berkeley.edu/news/media/releases/2007/02/12_IRE.shtm
23. Baker W and Heller J. "Material Selection for Transdermal Delivery Systems", In Transdermal Drug Delivery: Developmental Issues and Research Initiatives, J. Hadgraft and R.H. Guys, Eds. Marcel Dekker, Inc., New York 1989 pp. 293-311.
24. Wiechers J. Use of chemical penetration enhancers in Transdermal drug delivery-possibilities and difficulties. Acta pharm. 1992 : 4: 123.
25. Yamamoto T, Katakabe k, Akiyoshi K, Kan K and Asano T. Topical application of glibenclamide lowers blood glucose levels in rats. Diabetes res. Clin. Pract. 1990; 8: 19-22.
26. Al-Khamis K, Davis S.S and Hadgraft J. Microviscosity and drug release from topical gel formulations. Pharm. Res. 1986; 3: 214-217.
27. Anon. Transdermal delivery systems-general drug release standards. Pharmacopeial Forum, 1980; 14: 3860-3865.
28. Mayorga P, Puisieux F and Couarraze G. Formulation study of a Transdermal delivery system of primaquine. Int. J. pharm. 1996; 132: 71-79.
29. Deo M.R, Sant V.P, Parekh S.R, Khopade A.J and Banakar U.V. Proliposome-based Transdermal delivery of levonorgestrel. Jour. Biomat. Appl. 1997; 12: 77-88.
30. Yan-yu X, Yun- mei S, Zhi-Peng C and Qi-nerg P. Preparation of silymarin proliposomes; A new way to increase oral bioavailability of silymarin in beagle dogs. Int. pharm. 2006; 319: 162-168.
31. Crawford R.R and Esmerian O.K. Effect of plasticizers on some physical properties of cellulose acetate phthalate films. J. Pharm. Sci. 1997;60: 312- 314.
32. Shaila L, Pandey S and Udupa N. Design and evaluation of matrix type membrane controlled Transdermal drug delivery system of nicotin suitable for use in smoking cessation. Indian Journ. Pharm. Sci. 2006;68: 179-18
33. Aarti N, Louk A.R.M.P, Russel.O.P and Richard H.G. Mechanism of oleic acid induced skin permeation enhancement *in vivo* in humans. Jour. control. Release 1995; 37: 299-306.
34. Wade A and Weller P.J. Handbook of pharmaceutical Excipients. Washington, DC: American Pharmaceutical Publishing Association 1994; 362-366.
35. Lec S.T, Yac S.H, Kim S.W and Berner B. One way membrane for Transdermal drug delivery systems / system optimization. Int. J Pharm. 1991; 77: 231 - 237.
36. Vyas S.P and Khar R.K. Targetted and controlled Drug Delivery Novel carrier system 1st Ed., CBS Publishers and distributors, New Delhi, 2002; 411-447.
37. Singh J, Tripathi K.T and Sakia T.R. Effect of penetration enhancers on the *invitro* transport of ephedrine through rate skin and human epidermis from matrix based Transdermal formulations. Drug Dev. Ind. Pharm. 1993; 19: 1623-1628.